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(54) Title: ENDOTHELIN RECEPTOR-BINDING COMPOUNDS

(57) Abstract

Compounds of the formula (I): X_N-X_1-X_2-X_3-X_4-X_5-X_6-X_C are useful as agonists and antagonists of endothelin, where X_N is acyl or other N-terminal group, or a polypeptide of 1-50 amino acids; X_C is OH or other C-terminal group, or a polypeptide of 1-50 amino acids; and X_1-X_3 are each independently a peptide or peptoid, and X_4-X_6 are each independently a peptide, peptoid, or a bond, and at least one of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc.

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ENDOTHELIN RECEPTOR-BINDING COMPOUNDS

Description

Technical Field

This invention relates to biochemistry and pharmaceutical chemistry. More specifically, this invention relates to peptide and peptoid compounds which bind to endothelin receptors.

Background of the Invention

Endothelin-1 is a 21-amino acid peptide produced by vascular endothelial cells. Endothelin-2 and endothelin-3 are closely related peptides. Endothelin-1 has a potent vasoconstrictive effect and a sustained, potent pressor effect, which are mediated by binding of endothelins to their receptors.

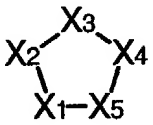
Increased endothelin levels are associated with cardiogenic shock, hypertension, pulmonary hypertension, acute myocardial infarction, uremia, Crohn's disease, ulcerative colitis, and is also observed following orthotopic liver transplantation and major abdominal surgical procedures. Endothelin may have a pathophysiologic role in sepsis, congestive heart failure, coronary spasm, cyclosporine nephrotoxicity, vasculitis, and pregnancy-associated toxemia.

Compounds which bind to endothelin receptors may act as agonists or antagonists, and modulate the conditions described above: A. Doherty, J Med Chem (1992) 35:1493-508. Several researchers have undertaken rational design of endothelin receptor-binding compounds: Hemmi *et al.*, EP 457,195; Kiyofumi *et al.*, EP 436,189. Sakurai *et al.*, EP 480,381 claimed cloning and expression of a mammalian endothelin receptor.

Disclosure of the Invention

We have now invented peptide and peptoid compounds which bind endothelin receptors. Compounds of the invention have the formula

$$X_N\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_C,$$

where X_N is lower acyl or other N-terminal group, or a polypeptide of 1-50 amino acids; X_C is OH or other C-terminal group, a polypeptide of 1-50 amino acids, or a protein; and X_1-X_3 are each independently a peptide or peptoid, and X_4-X_6 are each independently a peptide, peptoid, or a bond, and at least one of X_1-X_5 is selected from the group consisting of Ncys, Nthr, Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc. Another set of preferred compounds is that in which X_6 is a bond, and X_N together with X_C is a bond, thus forming a cyclic pentamer of the form 

. Another set of preferred compounds is that in which X_5-X_6 is a bond, thus forming a tetramer of the form X_N-X_1-X_2-X_3-X_4-X_C. Another set of preferred compounds is that in which X_4-X_5-X_6 is a bond, thus forming a trimer of the form X_N-X_1-X_2-X_3-X_C.

Another aspect of the invention is a pharmaceutical composition comprising a compound of the invention in combination with a pharmaceutically acceptable excipient.

Another aspect of the invention is a method for treating hypertension, by administering an effective amount of a compound of the invention.

Modes of Carrying Out The Invention

A. Definitions

The monomer abbreviations are as follows:

Ala = L-alanine (A);	βala = β-alanine (β);
Cys = L-cysteine (C);	Asp = L-aspartic acid (D);
Glu = L-glutamic acid (E);	Phe = L-phenylalanine (F);
Gly = glycine (G);	His = L-histidine (H);
Ile = L-isoleucine (I);	Lys = L-lysine (K);
Leu = L-leucine (L);	Met = L-methionine (M);
Asn = L-asparagine (N);	Pro = L-proline (P);
Gln = L-glutamine (Q);	Arg = L-arginine (R);
Ser = L-serine (S);	Thr = L-threonine (T);
Val = L-valine (V);	Trp = L-tryptophan (W);
Tyr = L-tyrosine (Y);	Orn = L-ornithine (O);
Nle = L-norleucine;	Aabu = α-aminobutyric acid;
Hphe = L-homophenylalanine;	Nva = L-norvaline;
Gabu = γ-aminobutyric acid;	Dala = D-alanine;
Dcys = D-cysteine;	Dasp = D-aspartic acid;
Dglu = D-glutamic acid;	Dphe = D-phenylalanine;
Dhis = D-histidine;	Dile = D-isoleucine;
Dlys = D-lysine;	Dleu = D-leucine;
Dmet = D-methionine;	Dasn = D-asparagine;
Dpro = D-proline;	Dgln = D-glutamine;
Darg = D-arginine;	Dser = D-serine;
Dthr = D-threonine;	Dval = D-valine;
Dtrp = D-tryptophan;	Dtyr = D-tyrosine;
Dorn = D-ornithine;	Aib = aminoisobutyric acid;
Etg = L-ethylglycine;	Tbug = L-*t*-butylglycine;
Pen = penicillamine;	Anap = α-naphthylalanine;
Chexa = cyclohexylalanine;	Cpen = cyclopentylalanine;
Cpro = aminocyclopropane carboxylate;	Norb = aminonorbornylcarboxylate.

Amino acids having an α-methyl group are abreviated Mxxx, where xxx is the multi-letter abbreviation for the amino acid that has the corresponding side chain:

Mala = L-α-methylalanine;	Mcys = L-α-methylcysteine;
Masp = L-α-methylaspartic acid;	Mglu = L-α-methylglutamic acid;
Mphe = L-α-methylphenylalanine;	Mhis = L-α-methylhistidine;
Mile = L-α-methylisoleucine;	Mlys = L-α-methyllysine;
Mleu = L-α-methylleucine;	Mmet = L-α-methylmethionine;
Masn = L-α-methylasparagine;	Mpro = L-α-methylproline;
Mgln = L-α-methylglutamine;	Marg = L-α-methylarginine;
Mser = L-α-methylserine;	Mthr = L-α-methylthreonine;
Mval = L-α-methylvaline;	Mtrp = L-α-methyltryptophan;
Mtyr = L-α-methyltyrosine;	Morn = L-α-methylornithine;
Mnle = L-α-methylnorleucine;	Maabu = α-amino-α-methylbutyric acid;

Mnva = L-α-methylnorvaline; Mhphe = L-α-methylhomophenylalanine;
Metg = L-α-methylethylglycine; Mgabu = α-methyl-γ-aminobutyric acid;
Maib = α-methylaminoisobutyric acid; Mtbug = L-α-methyl-*t*-butylglycine;
Mpen = α-methylpenicillamine; Manap = α-methyl-α-naphthylalanine;
Mchexa = α-methylcyclohexylalanine; Mcpen = α-methylcyclopentylalanine.

D-Amino acids having an α-methyl group are abreviated Dmxxx, where xxx is the multi-letter abbreviation for the amino acid that has the corresponding side chain:

Dmala = D-α-methylalanine; Dmorn = D-α-methylornithine;
Dmcys = D-α-methylcysteine; Dmasp = D-α-methylaspartic acid;
Dmglu = D-α-methylglutamic acid; Dmphe = D-α-methylphenylalanine;
Dmhis = D-α-methylhistidine; Dmile = D-α-methylisoleucine;
Dmlys = D-α-methyllysine; Dmleu = D-α-methylleucine;
Dmmet = D-α-methylmethionine; Dmasn = D-α-methylasparagine;
Dmpro = D-α-methylproline; Dmgln = D-α-methylglutamine;
Dmarg = D-α-methylarginine; Dmser = D-α-methylserine;
Dmthr = D-α-methylthreonine; Dmval = D-α-methylvaline;
Dmtrp = D-α-methyltryptophan; Dmtyr = D-α-methyltyrosine.

L-Amino acids having a methyl group on the amide nitrogen are designated Nmxxx, where xxx is the multi-letter abbreviation for the amino acid that has the corresponding side chain:

Nmala = L-N-methylalanine; Nmcys = L-N-methylcysteine;
Nmasp = L-N-methylaspartic acid; Nmglu = L-N-methylglutamic acid;
Nmphe = L-N-methylphenylalanine; Nmhis = L-N-methylhistidine;
Nmile = L-N-methylisoleucine; Nmlys = L-N-methyllysine;
Nmleu = L-N-methylleucine; Nmmet = L-N-methylmethionine;
Nmasn = L-N-methylasparagine; Nmchexa = N-methylcyclohexylalanine;
Nmgln = L-N-methylglutamine; Nmarg = L-N-methylarginine;
Nmser = L-N-methylserine; Nmthr = L-N-methylthreonine;
Nmval = L-N-methylvaline; Nmtrp = L-N-methyltryptophan;
Nmtyr = L-N-methyltyrosine; Nmorn = L-N-methylornithine;
Nmnle = L-N-methylnorleucine; Nmaabu = N-amino-α-methylbutyric acid;
Nmnva = L-N-methylnorvaline; Nmhphe = L-N-methylhomophenylalanine;
Nmetg = L-N-methylethylglycine; Nmgabu = N-methyl-γ-aminobutyric acid;
Nmcpen = N-methylcyclopentylalanine; Nmtbug = L-N-methyl-*t*-butylglycine;
Nmpen = N-methylpenicillamine; Nmanap = N-methyl-α-naphthylalanine;
Nmaib = N-methylaminoisobutyric acid.

D-Amino acids having an N-methyl group are abreviated Dnmxxx, where xxx is the multi-letter abbreviation for the amino acid that has the corresponding side chain:

Dnmala = D-N-methylalanine; Dnmorn = D-N-methylornithine;
Dnmcys = D-N-methylcysteine; Dnmasp = D-N-methylaspartic acid;
Dnmglu = D-N-methylglutamic acid; Dnmphe = D-N-methylphenylalanine;
Dnmhis = D-N-methylhistidine; Dnmile = D-N-methylisoleucine;

Dnmlys = D-N-methyllysine; Dnmleu = D-N-methylleucine;
Dnmmet = D-N-methylmethionine; Dnmasn = D-N-methylasparagine;
Dnmpro = D-N-methylproline; Dnmgln = D-N-methylglutamine;
Dnmarg = D-N-methylarginine; Dnmser = D-N-methylserine;
Dnmthr = D-N-methylthreonine; Dnmval = D-N-methylvaline;
Dnmtrp = D-N-methyltryptophan; Dnmtyr = D-N-methyltyrosine.

N-substituted glycine monomers are named Nxxx, where xxx is the multi-letter abbreviation for the amino acid that has the corresponding side chain. An "h" indicates that the monomer is a homolog, having an additional -CH_2- between the nitrogen atom and the rest of the side chain (*e.g.*, Nhhis has imidazolylethyl rather than imidazolylmethyl as its side chain):

Nala = N-methylglycine (sarcosine); Nasp = N-(carboxymethyl)glycine;
Nglu = N-(2-carboxyethyl)glycine; Nphe = N-benzylglycine;
Nhhis = N-(imidazolylethyl)glycine; Nile = N-(1-methylpropyl)glycine;
Nlys = N-(4-aminobutyl)glycine; Nleu = N-(2-methylpropyl)glycine;
Nmet = N-(2-methylthioethyl)glycine; Nhser = N-(hydroxyethyl)glycine;
Nasn = N-(carbamylmethyl)glycine; Ngln = N-(2-carbamylethyl)glycine;
Nval = N-(1-methylethyl)glycine; Narg = N-(3-guanidinopropyl)glycine;
Nhtrp = N-(3-indolylethyl)glycine; Nhtyr = N-(p-hydroxyphenethyl)glycine;
Nthr = N-(1-hydroxyethyl)glycine; Ncys = N-(thiomethyl)glycine; and
Norn = N-(3-aminopropyl)glycine.

Additional monomers useful in the practice of the invention are:

Ncpro = N-cyclopropylglycine;
Ncbut = N-cyclobutylglycine;
Nchex = N-cyclohexylglycine;
Nchep = N-cycloheptylglycine;
Ncoct = N-cyclooctylglycine;
Ncdec = N-cyclodecylglycine;
Ncund = N-cycloundecylglycine;
Ncdod = N-cyclododecylglycine;
Nbhm = N-(2,2-diphenylethyl)glycine;
Nbhe = N-(3,3-diphenylpropyl)glycine;
Nnbhm = N-(N-(2,2-diphenylethyl)carbamylmethyl)glycine;
Nnbhe = N-(N-(3,3-diphenylpropyl)carbamylmethyl)glycine;
Nbmc = 1-carboxy-1-(2,2-diphenylethylamino)cyclopropane; and
Naeg = N-(2-aminoethyl)glycine.

The terms "peptide" and "conventional amino acid" as used herein refers to the twenty amino acids directly encoded by the genetic code, *i.e.*, alanine (A), cysteine (C), aspartic acid (D), glutamic acid (E), phenylalanine (F), glycine (G), histidine (H), isoleucine (I), lysine (K), leucine (L), methionine (M), asparagine (N), proline (P),

glutamine (Q), arginine (R), serine (S), threonine (T), valine (V), tryptophan (W), and tyrosine (Y).

The term "peptoid" refers to monomers other than the twenty conventional amino acids and the common nucleotides and nucleosides (*i.e.*, the DNA bases dA, dC, dG, and dT, and the RNA bases A, C, G, and U). The terms "amide peptoid" and nonconventional amino acid" refer to peptoids which are linked together through amide (peptide) bonds. Amide polypeptoid bonds may include substituents on the amide nitrogen atom. Presently preferred peptoids include Aabu, Aib, Anap, βala, Chexa, Cpen, Cpro, Dala, Darg, Dasn, Dasp, Dcys, Dgln, Dglu, Dhis, Dile, Dleu, Dlys, Dmala, Dmarg, Dmasn, Dmasp, Dmcys, Dmet, Dmgln, Dmglu, Dmhis, Dmile, Dmleu, Dmlys, Dmmet, Dmorn, Dmphe, Dmpro, Dmser, Dmthr, Dmtrp, Dmtyr, Dmval, Dnmala, Dnmarg, Dnmasn, Dnmasp, Dnmcys, Dnmgln, Dnmglu, Dnmhis, Dnmile, Dnmleu, Dnmlys, Dnmmet, Dnmorn, Dnmphe, Dnmpro, Dnmser, Dnmthr, Dnmtrp, Dnmtyr, Dnmval, Dorn, Dphe, Dpro, Dser, Dthr, Dtrp, Dtyr, Dval, Etg, Gabu, Hphe, Maabu, Maib, Mala, Manap, Marg, Masn, Masp, Mchexa, Mcpen, Mcys, Metg, Mgabu, Mgln, Mglu, Mhis, Mhphe, Mile, Mleu, Mlys, Mmet, Mnle, Mnva, Morn, Mpen, Mphe, Mpro, Mser, Mtbug, Mthr, Mtrp, Mtyr, Mval, Naeg, Nala, Narg, Nasn, Nasp, Nbhe, Nbhm, Nbmc, Ncbut, Ncdec, Ncdod, Nchep, Nchex, Ncoct, Ncpro, Ncund, Ncys, Ngln, Nglu, Nhhis, Nhser, Nhtrp, Nhtyr, Nile, Nle, Nleu, Nlys, Nmaabu, Nmaib, Nmala, Nmanap, Nmarg, Nmasn, Nmasp, Nmchexa, Nmcpen, Nmcys, Nmet, Nmetg, Nmgabu, Nmgln, Nmglu, Nmhis, Nmhphe, Nmile, Nmleu, Nmlys, Nmmet, Nmnle, Nmnva, Nmorn, Nmpen, Nmphe, Nmser, Nmtbug, Nmthr, Nmtrp, Nmtyr, Nmval, Nnbhe, Nnbhm, Norb, Norn, Nphe, Nthr, Nva, Nval, Orn, Pen, and Tbug.

The term "treatment" as used herein refers to reducing or alleviating symptoms in a subject, preventing symptoms from worsening or progressing, inhibition or elimination of the causative agent, or prevention of the infection or disorder in a subject who is free therefrom. Thus, for example, treatment of a cancer patient may be reduction of tumor size, elimination of malignant cells, prevention of metastasis, or the prevention of relapse in a patient who has been cured. Treatment of infection includes destruction of the infecting agent, inhibition of or interference with its growth or maturation, neutralization of its pathological effects, and the like. Treatment of hyper-

tension includes reducing systolic and/or diastolic blood pressure, in addition to arresting increasing blood pressure or reducing the rate of blood pressure increase due to other causes.

The term "hyperproliferative disorder" refers to disorders characterized by an abnormal or pathological proliferation of cells, for example, cancer, psoriasis, atherosclerosis, hyperplasia and the like.

The term "lower alkyl" as used herein refers to straight, branched, and cyclic chain hydrocarbon radicals having from 1 to 8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, *n*-hexyl, cyclopentyl, cyclohexyl, 2-methylcyclopentyl, cyclopentylacetyl, and the like. "Lower alkoxy" refers to radicals of the formula -OR, where R is lower alkyl as defined above. "Aryl" refers to aromatic hydrocarbons having up to 14 carbon atoms, preferably phenyl or naphthyl. "Aryl-lower alkyl" refers to radicals of the form Ar-R-, where Ar is aryl and R is lower alkyl.

The term "lower acyl" refers to a radical of the formula RCO-, in which R is H, lower alkyl as defined above, phenyl or benzyl. Exemplary lower acyl groups include acetyl, propionyl, formyl, *t*-butoxycarbonyl, benzoyl, and the like.

The term "N-terminal group" (X_N) includes peptides and proteins, solid supports, lower acyl moieties, urea derivatives (*e.g.*, cyclohexylurea, ethylurea, *t*-butylurea, and the like), succinyl, 9-fluorenylmethoxycarbonyl, trimethylsilylethoxycarbonyl, and other groups suitable for use peptide N-terminal protecting groups.

The term "C-terminal group" (X_C) includes peptides and proteins, solid supports, OH, NH_2, lower alkyl esters, lower alkyl amides, and other groups suitable for use peptide C-terminal protecting groups.

The term "effective amount" refers to an amount of compound sufficient to exhibit a detectable therapeutic effect. The therapeutic effect may include, for example, without limitation, inhibiting the replication of pathogens, inhibiting or preventing the release of toxins by pathogens, killing pathogens, and preventing the establishment of infection (prophylaxis). The precise effective amount for a subject will depend upon the subject's size and health, the nature of the pathogen, the severity of the

infection, and the like. Thus, it is not possible to specify an exact effective amount in advance. However, the effective amount for a given situation can be determined by routine experimentation based on the information provided herein.

The phrase "indication modulated by endothelin" refers to a pathological condition which is caused by, or ameliorated by, endothelin. Indications modulated by endothelin are responsive to either endothelin agonists or endothelin antagonists, depending on whether the condition is caused by excessive endothelin effects or insufficiency. Examples of suitable conditions include hypertension, congestive heart failure, endotoxic shock, pulmonary carcinoma, arrhythmia, asthma, cerebral vasospasm, subarachnoid hemorrhage, and the like.

The term "pharmaceutically acceptable" refers to compounds and compositions which may be administered to mammals without undue toxicity. Exemplary pharmaceutically acceptable salts include mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like.

B. General Method

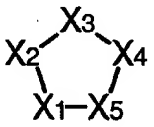
Compounds of the invention have the formula

$$X_N\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_C,$$

where X_N is an N-terminal group; X_C is a C-terminal group, a polypeptide of 1-50 amino acids or a protein; X_1-X_3 are each independently a peptide or peptoid, and X_4-X_6 are each independently a peptide, peptoid, or a bond, and at least one of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc. Preferred compounds of the invention are those where X_N is lower acyl, cyclopentylacetyl, benzyloxycarbonyl, *t*-butoxycarbonyl, succinyl, 9-fluorenylmethoxycarbonyl, or trimethylsilylethoxycarbonyl, or a polypeptide chain of 1-50 amino acids; X_C is OH, NH_2, an ester or amide, or a polypeptide chain of 1-50 amino acids or a protein; and X_1, X_2, X_3, X_4, X_5, X_6 are each independently Aabu, Aib, Ala, Anap, Arg, Asn, Asp, Chexa, Cpen, Cpro, Cys, Dala, Darg, Dasn, Dasp, Dcys, Dgln, Dglu, Dhis, Dile, Dleu, Dlys, Dmala, Dmarg, Dmasn, Dmasp, Dmcys, Dmet, Dmgln, Dmglu, Dmhis,

Dmile, Dmleu, Dmlys, Dmmet, Dmorn, Dmphe, Dmpro, Dmser, Dmthr, Dmtrp, Dmtyr, Dmval, Dnmala, Dnmarg, Dnmasn, Dnmasp, Dnmcys, Dnmgln, Dnmglu, Dnmhis, Dnmile, Dnmleu, Dnmlys, Dnmmet, Dnmorn, Dnmphe, Dnmpro, Dnmser, Dnmthr, Dnmtrp, Dnmtyr, Dnmval, Dorn, Dphe, Dpro, Dser, Dthr, Dtrp, Dtyr, Dval, Etg, Gabu, Gln, Glu, Gly, His, Hphe, Ile, Leu, Lys, Maabu, Maib, Mala, Manap, Marg, Masn, Masp, Mchexa, Mcpen, Mcys, Met, Metg, Mgabu, Mgln, Mglu, Mhis, Mhphe, Mile, Mleu, Mlys, Mmet, Mnle, Mnva, Morn, Mpen, Mphe, Mpro, Mser, Mtbug, Mthr, Mtrp, Mtyr, Mval, Naeg, Nala, Narg, Nasn, Nasp, Nbhe, Nbhm, Nbmc, Ncbut, Ncdec, Ncdod, Nchep, Nchex, Ncoct, Ncpro, Ncund, Ncys, Ngln, Nglu, Nhhis, Nhser, Nhtrp, Nhtyr, Nile, Nle, Nleu, Nlys, Nmaabu, Nmaib, Nmala, Nmanap, Nmarg, Nmasn, Nmasp, Nmchexa, Nmcpen, Nmcys, Nmet, Nmetg, Nmgabu, Nmgln, Nmglu, Nmhis, Nmhphe, Nmile, Nmleu, Nmlys, Nmmet, Nmnle, Nmnva, Nmorn, Nmpen, Nmphe, Nmser, Nmtbug, Nmthr, Nmtrp, Nmtyr, Nmval, Nnbhe, Nnbhm, Norb, Norn, Nphe, Nthr, Nva, Nval, Orn, Pen, Phe, Pro, Ser, Tbug, Thr, Trp, Tyr, or Val. A preferred class of the invention comprises those compounds wherein X_3 is selected from the group consisting of Asp and Dasp, particularly where X_4 and X_5 are each independently selected from the group consisting of Aabu, Ala, Dile, Dmet, Dval, Ile, Met, Nle, Trp, and Val. A preferred subclass comprises those compounds wherein X_6 is selected from the group consisting of Dtrp, Gly, and Trp, particularly where X_2 is selected from the group consisting of Aabu, Ala, Arg, Asn, Asp, Cys, Darg, Dasn, Dcys, Dgln, Dglu, Dorn, Dphe, Dphe, Dser, Dtyr, Dval, Gabu, Gly, His, His, Hphe, Ile, Leu, Lys, Nasp, Nglu, Nhhis, Naeg, Nleu, Nphe, Nva, Orn, Pro, Ser, Thr, Trp, Tyr, and Val. Presently preferred compounds of the invention are X_N-Dphe-Ala-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Asn-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Cys-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Dcys-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Dorn-Asp-Dile-Dile-Dtrp-X_C, X_N-Dphe-Dorn-Asp-Dile-Ile-Dtrp-X_C, X_N-Dphe-Dorn-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Dorn-Dasp-Dile-Ile-Dtrp-X_C, X_N-Dphe-Dorn-Dasp-Ile-Ile-Trp-X_C, **X_N-Dphe-Dphe-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Dtyr-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Hphe-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Nglu-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Nleu-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Nphe-Asp-Ile-Ile-Trp-X_C, $_N$-Dphe-Orn-Asp-Dile-Ile-Trp-X_C, X_N-Dphe-Orn-Asp-Ile-Dile-Dtrp-X_C, X_N-Dphe-Orn-Asp-Ile-Ile-Dtrp-X_C, X_N-Dphe-Orn-Asp-Ile-Dile-Trp-X_C, X_N-Dphe-Orn-Asp-Nva-Ile-Trp-X_C, X_N-Dphe-Orn-

Dasp-Ile-Dile-Trp-X_C, X_N-Dphe-Orn-Dasp-Ile-Ile-Trp-X_C, X_N-Dphe-Pro-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Trp-Asp-Ile-Ile-Trp-X_C, X_N-Dphe-Tyr-Asp-Ile-Ile-Trp-X_C, X_N-Dtrp-Nphe-Asp-Ile-Ile-Trp-X_C, X_N-Phe-Dorn-Dasp-Dile-Ile-Trp-X_C, X_N-Phe-Orn-Asp-Ile-Ile-Trp-X_C, X_N-Phe-Orn-Dasp-Ile-Ile-Trp-X_C, particularly where X_N is acetyl and X_C is OH.

Another set of preferred compounds is that in which X_N together with X_6-X_C is a bond, thus forming a cyclic pentamer of the form 

. Preferred compounds of the invention include at least one amide peptoid monomer (N-substituted glycine) in the sequence. A presently preferred subclass of this set is those compounds wherein X_1 is Dtrp or Nhtrp, X_2 is Dasp or Nasp, and X_3 is Pro. Presently preferred compounds of this form are cyclo[Dtrp-Dasp-Pro-Nleu-Lval], cyclo[Dtrp-Dasp-Pro-Nphe-Lval], cyclo[Dtrp-Dasp-Pro-Dval-Nleu], cyclo[Dtrp-Dasp-Pro-Dval-Nphe], cyclo[Nleu-Dasp-Pro-Dval-Nleu], and cyclo[Nphe-Dasp-Pro-Dval-Nleu].

Another set of preferred compounds is that in which X_5-X_6 is a bond, thus forming a tetramer of the form X_N-X_1-X_2-X_3-X_4-X_C. A preferred subclass of these compounds has the formula X_N-X_1-Lval-Dtrp-X_4-X_C.

Another set of preferred compounds is that in which X_4-X_5-X_6 is a bond, thus forming a trimer of the form X_N-X_1-X_2-X_3-X_C. One preferred subclass is the set of compounds wherein X_2 is Dtrp and X_3 is βala or Dtrp. Another preferred subclass is the set of compounds wherein X_1 is Leu and X_3 is βala or Dtrp. Another preferred subclass is the set of compounds wherein X_1 is Leu and X_2 is Dtrp.

Compounds of the invention are synthesized employing techniques known in the art for polypeptide synthesis, and may be prepared using standard polypeptide synthesis devices. One may synthesize compounds of the invention by recombinant methods, by chemical synthetic methods, and/or a combination of the two. Recombinant expression techniques are preferred for molecules which consist predominantly of conventional amino acids, or which may be modified post-expression to obtain the desired compounds. Compounds which comprise large regions of consec-

utive conventional amino acids may be synthesized by hybrid methods, *i.e.*, by expressing the conventional regions, adding suitable protecting groups, and attaching the non-conventional amino acids. Compounds which are predominantly monomers other than conventional amino acids are preferably prepared entirely by chemical synthetic methods.

Chemical methods may employ solid phase or solution-phase techniques. Suitable synthetic methods include, for example, those described in A.M. Gray *et al.*, J Org Chem (1991) 56:6659-66, R.M. Valerio *et al.*, Anal Biochem (1991) 197:168-77, and H.M. Geysen *et al.*, J Immunol Meth (1987) 102:259-74.

Monomers used to prepare compounds of the invention may be obtained from commercial sources, or may be prepared by methods known in the art, *e.g.*, as disclosed in EP 457,195, EP 436,189, and Bartlett *et al.*, WO91/19735 (incorporated herein by reference in full), *inter alia.*

Endothelin activity is mediated by the binding of endothelin to one of its two cell surface receptors, designated type A (ETR_A) and type B (ETR_B). Compounds which bind to one or both receptors therefor may exhibit either agonistic or antagonistic activity, depending on whether binding of the compound effects or blocks activation of the receptor.

Endothelin receptor (ETR) binding may be assayed *in vitro* using methods known in the art. For example, one may culture cells which express ETR_A or ETR_B on their surface, and detect mitogenicity, Ca^{2+} influx, *c-fos* or *c-myc* activation, and the like. Simple binding may be detected by measuring competition for labeled endothelin, *e.g.*, ^{125}I-endothelin (available commercially from DuPont/New England Nuclear). One may employ cells which normally express ETR, or may use cells which have been transfected or infected with the desired ETR gene. N. Takuwa *et al.*, J Biol Chem (1989) 264:7856-61 describes a suitable assay for ETR_A binding which uses cultured Swiss 3T3 fibroblasts and detects binding to endogenous ETR_A by the increased intracellular Ca^{2+} (using the Ca^{2+}-sensitive fluorescent indicator fura-2). M. Clozel *et al.*, J Clin Invest (1989) 83:1758-61 disclosed a suitable assay for human ETR_A binding using human vascular smooth muscle cells. One may also employ the assay methods

described by Hemmi *et al.*, EP 457,195, and Kiyofumi *et al.*, EP 436,189, both incorporated herein by reference.

ETR_A and ETR_B binding activity may be demonstrated using recombinantly expressed receptor. Cloning of ETR_B was reported by M. Nakamuta *et al.*, Biochem Biophys Res Commun (1991) 177:34-39. See also Sakurai *et al.*, EP 480,381. The receptor is preferably expressed in eukaryotic cells, for example using the baculovirus expression system described by Summers and Smith. Generally, the components of the expression system include a transfer vector, usually a bacterial plasmid, which contains both a fragment of the baculovirus genome, and a convenient restriction site for insertion of the heterologous gene or genes to be expressed; a wild-type baculovirus with a sequence homologous to the baculovirus-specific fragment in the transfer vector (which allows for the homologous recombination of the heterologous gene in to the baculovirus genome); and appropriate insect host cells and growth media.

After inserting the DNA sequence encoding the ETR into the transfer vector, the vector and the wild type viral genome are transfected into an insect host cell where the vector and viral genome are allowed to recombine. The packaged recombinant virus is expressed and recombinant plaques are identified and purified. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *inter alia*, Invitrogen, San Diego CA ("MaxBac" kit). These techniques are generally known to those skilled in the art and fully described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987) (hereinafter "Summers and Smith"). Currently, the most commonly used transfer vector for introducing foreign genes into AcNPV is pAcC13 (S. Munemitsu *et al.*, Mol Cell Biol (1990) 10:5977-82). Many other vectors, known to those of skill in the art, have also been designed. These include, for example, pVL985 (which alters the polyhedrin start codon from ATG to ATT, and which introduces a BamHI cloning site 32 basepairs downstream from the ATT; see Luckow and Summers, Virology (1989) 17:31.

Recombinant baculovirus expression vectors have been developed for infection into several insect cells. For example, recombinant baculoviruses have been developed for, *inter alia*: *Aedes aegypti*, *Autographa californica*, *Bombyx mori*, *Drosophila melanogaster*, *Spodoptera frugiperda*, and *Trichoplusia ni* (PCT WO89/046699;

Carbonell *et al.*, J Virol (1985) 56:153; Wright, Nature (1986) 321:718; Smith *et al.*, Mol Cell Biol (1983) 3:2156; and see generally, Fraser, *et al.*, In Vitro Cell Dev Biol (1989) 25:225). Cells and cell culture media are commercially available for both direct and fusion expression of heterologous polypeptides in a baculovirus/expression system; cell culture technology is generally known to those skilled in the art. See *e.g.*, Summers and Smith above. ETR_B binding may be assayed directly on the cell surface.

Alternatively, one may assay ETR binding using isolated ETR, either in soluble (*e.g.*, truncated) form, or immobilized on a solid support.

The compounds of the invention may be administered by a variety of methods, such as intravenously, orally, intramuscularly, intraperitoneally, bronchially, intranasally, and so forth. The preferred route of administration will depend upon the nature of the compound and the condition to be treated. Compounds may be administered orally if well absorbed and not substantially degraded upon ingestion. The compounds may be administered as pharmaceutical compositions in combination with a pharmaceutically acceptable excipient. Such compositions may be aqueous solutions, emulsions, creams, ointments, suspensions, gels, liposomal suspensions, and the like. Thus, suitable excipients include water, saline, Ringer's solution, dextrose solution, and solutions of ethanol, glucose, sucrose, dextran, mannose, mannitol, sorbitol, polyethylene glycol (PEG), phosphate, acetate, gelatin, collagen, Carbopol®, vegetable oils, and the like. One may additionally include suitable preservatives, stabilizers, antioxidants, antimicrobials, and buffering agents, for example, BHA, BHT, citric acid, ascorbic acid, tetracycline, and the like. Cream or ointment bases useful in formulation include lanolin, Silvadene® (Marion), Aquaphor® (Duke Laboratories), and the like. Other topical formulations include aerosols, bandages, sustained-release patches, and the like. Alternatively, one may incorporate or encapsulate the compound in a suitable polymer matrix or membrane, thus providing a sustained-release delivery device suitable for implantation near the site to be treated locally. Other devices include indwelling catheters and devices such as the Alzet® minipump. Further, one may provide the compound in solid form, especially as a lyophilized powder. Lyophilized formulations typically contain stabilizing and bulking agents, for example human serum albumin, sucrose,

mannitol, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in Remington's Pharmaceutical Sciences (Mack Pub. Co.).

C. Examples

The examples presented below are provided as a further guide to the practitioner of ordinary skill in the art, and are not to be construed as limiting the invention in any way.

Example 1

(Synthesis of Trimer, Tetramer, and Hexamer Polypeptoids)

(A) Chemical Synthesis of Polypeptoids

Polyethylene pins were prepared for peptide synthesis as described by F.S. Tjöeng *et al.*, Int J Peptide Protein Res (1990) 35:141-46. Compounds were synthesized using N^{α}-Fmoc protected monomers.

The C-terminal monomer was incorporated as the preformed ester. The ester was coupled to Boc-deprotected pins with DCC:HOBt (1.2:2) at 27°C for 2 hours. Coupling reactions were performed with N^{α}-Fmoc protected monomers in polypropylene microtitre plates as described by Geysen *et al.* to provide trimers, tetramers, and hexamers, as desired. When complete, side chains were deprotected with TFA/anisole/ethanedithiol (95:2.5:2.5) for 4 hours. The pins were then air dried, sonicated in 0.1% HCl in MeOH/H_2O (1:1) for 15 minutes, washed in EtOH for 30 minutes, and dried under vacuum.

Compounds were cleaved from the pins using 0.3% NaOH (EtOH/H_2O, 1:1) for 30 minutes, followed by neutralization with 0.6 M NaH_2PO_4. The resulting compounds were dried under vacuum.

(B) Determination of Activity

Hexamers prepared in part A) above were assayed for ability to compete with ^{125}I-endothelin-1 for binding to Swiss 3T3 fibroblasts (ETR_A), as described by N. Takuwa *et al.*, J Biol Chem (1989) 264:7856-61. The results for a selection of compounds were as follows:

X_N	X_1	X_2	X_3	X_4	X_5	X_6-X_C	IC_{50} (μM)
Ac	Dtrp	Nphe	Asp	Ile	Ile	Trp-OH	0.005
Ac	Dphe	Nphe	Asp	Ile	Ile	Trp-OH	0.012
Ac	Dtrp	Orn	Asp	Ile	Ile	Trp-OH	0.015
Ac	Dtyr	Orn	Asp	Ile	Ile	Trp-OH	0.03
Ac	Dphe	Pro	Asp	Ile	Ile	Trp-OH	0.04
Ac	Dphe	Ala	Asp	Ile	Ile	Trp-OH	0.06
Ac	Dphe	Hphe	Asp	Ile	Ile	Trp-OH	0.07
Ac	Dphe	Asn	Asp	Ile	Ile	Trp-OH	0.08
Ac	Dphe	Tyr	Asp	Ile	Ile	Trp-OH	0.08
Ac	Dphe	Trp	Asp	Ile	Ile	Trp-OH	0.08
Ac	Dphe	Dphe	Asp	Ile	Ile	Trp-OH	0.09
Ac	Dphe	Dtyr	Asp	Ile	Ile	Trp-OH	0.11
Ac	Dphe	Orn	Asp	Nva	Ile	Trp-OH	0.11
Ac	Dphe	Orn	Asp	Ile	Ile	Trp-OH	0.23
Ac	Dphe	Phe	Asp	Ile	Ile	Trp-OH	0.27
Ac	Dphe	Nleu	Asp	Ile	Ile	Trp-OH	0.28
Ac	Dphe	Cys	Asp	Ile	Ile	Trp-OH	0.31
Ac	Dphe	Nglu	Asp	Ile	Ile	Trp-OH	0.36
Ac	Dphe	Dcys	Asp	Ile	Ile	Trp-OH	0.41
Ac	Dphe	Orn	Asp	Ile	Ile	Trp-OH	1.00

C) Several hexamers prepared in part A) above were assayed for binding to ETR_B expressed recombinantly on live Sf9 cells using a baculovirus expression system. The results for a selection of compounds were as follows:

X_N	X_1	X_2	X_3	X_4	X_5	X_6-X_C	IC_{50} (μM)
Ac	Dtrp	Nphe	Asp	Ile	Ile	Trp-OH	0.20
Ac	Dphe	Nphe	Asp	Ile	Ile	Trp-OH	4.0

Example 2

(Synthesis of Cyclic Pentamer Peptoids)

(A) Preparation of cyclo[Dtrp-Dasp-Pro-Nleu-Dval]

4-(2',4'-Dimethoxyphenylhydroxymethyl)phenoxy resin, Rink super acid labile resin (100-200 mesh, 1% crosslinked with divinylbenzene) was obtained from Calbiochem (San Diego, CA). Other chemicals for peptoid synthesis were obtained from Advanced Chemtech (Lexington, KY) or Novabiochem (San Diego, CA) and used as received. N-substituted glycine monomers were prepared as described by Bartlett *et al.*, WO91/19735. FAB mass spectra were obtained in either nitrobenzyl alcohol or

thioglycerol matrices at the University of California mass spectrometry facilities (Berkeley, CA), or at Mass Search (Modesto, CA).

The resin (1 g, 0.53 mmol/g) was treated with FMOC-Dval (902 mmol, 2.66 mmol) in 8 mL DMF, followed by DIEA (125 µL, 0.72 mmol), DIC (diisopropyl-carbodiimide) (6 mL of 0.5 M solution in DCM), and DMAP (dimethylaminopyridine, 20 mg) for 4 hours at room temperature. After draining and rinsing, the unreacted amino groups were capped with benzoic anhydride (1 g) in 10 mL pyridine (20%) and DMF (80%). The substitution level was 0.44 mmol/g.

PyBOP was used in the subsequent steps for synthesis of all compounds. The N-terminal FMOC group was removed by treatment with 20% piperidine/DMF for 15 minutes. Then, the Fmoc monomer (Dasp), PyBOP, and 1-hydroxybenzotriazole (HOBt) were added in a 5-fold molar excess to resin-bound amino groups at a final concentration of 0.3 M each, in DMF (N,N-dimethylformamide). Diisopropylethylamine (DIEA) was then added to a final concentration of 0.6 M. The reaction was allowed to proceed for 30 min at room temperature with mixing provided by an intermittent stream of argon through the frit of the reaction vessel. The acylation was repeated, and the unreacted amines were capped with acetic anhydride. Monomer addition was repeated until the pentamer H-Dtrp-Dasp(O*t*Bu)-Pro-Nleu-Dval-OH was obtained.

The resin sample (500 mg, 0.10 mmol) was then treated with DCM (5 mL), followed by 1% TFA/DCM (5 mL). The resin was incubated with 1% TFA for 2 minutes and then filtered into 10% pyridine/methanol (1 mL). The TFA treatment was repeated 3 times. The filtrates were then combined and concentrated *in vacuo* to yield 160 mg of crude product. HPLC characterization of the compound was performed with a C4 reversed-phase column (Vydac 4.6 × 250 mm), using a 0.8 mL/min flow rate, a gradient elution with eluants, buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN and a linear gradient of 5-65% buffer B in 30 min. Detection was performed at 214 and 280 nm. The crude product (R_t = 28.3 min) was obtained in ~60% purity.

The crude peptoid (H-Dtrp-Dasp(O*t*Bu)-Pro-Nleu-Dval-OH) was dissolved in 10% DMF/H_2O (5 mL) and loaded onto a C4 reversed-phase column (Vydac, 22 × 250 mm). A 9.5 mL/min flow rate and a linear gradient of 10-55% buffer B in 45

min were used. The product (R_t = 23.2 min) was then lyophilized to give 7.5 mg (12% yield) of a white powder. MS m/z 667.5 (MH)+.

The purified linear peptoid (H-Dtrp-Dasp(O*t*Bu)-Pro-Nleu-Dval-OH) (7.2 mg, 11 µmol) was dissolved in 5 mL of DMF. PyBOP (15 mg, 29 µmol), 0.5 M HOBt/ DMF (60 µL, 30 µmol) and DIEA (10.5 µL, 60 µmol) were then added. The solution was mixed gently for 24 hr at room temperature. The reaction was monitored by HPLC using the analytical conditions set forth above. Formation of the cyclic pentapeptoid (R_t = 29.3 min) was complete after 24 hr. The solvent was then evaporated *in vacuo* to give 1 mL of crude product as a brown oil.

The crude cyclic peptoid, cyclo[Dtrp-Dasp(O*t*Bu)-Pro-Nleu-Dval] was treated with 90% TFA/H_2O (2 mL) for 20 min at room temperature. The deprotection product was characterized by analytical HPLC (R_t = 24.4 min) using the conditions stated above. The solvent was then removed *in vacuo* to give 7.2 mg (11% yield) of crude product as an oil.

The crude compound cyclo[Dtrp-Dasp-Pro-Nleu-Dval] was dissolved in 50% HOAc/H_2O (10 mL) and loaded onto a C4 column (Vydac, 10 x 250 mm). A 4.5 mL/min flow rate and a linear gradient of 10-45% buffer B in 50 min were used. The product (R_t = 25.9 min) was then lyophilized to give 2 mg of a white fluffy powder. The product purity was >90% by the analytical HPLC conditions stated above. MS mz 611.3 (MH)+.

(B) Synthesis of Additional Compounds

Proceeding as described in part (A) above, but substituting the monomers Aabu, Aib, Ala, Anap, Arg, Asn, Asp, Chexa, Cpen, Cpro, Cys, Dala, Darg, Dasn, Dasp, Dcys, Dgln, Dglu, Dhis, Dile, Dleu, Dlys, Dmala, Dmarg, Dmasn, Dmasp, Dmcys, Dmet, Dmgln, Dmglu, Dmhis, Dmile, Dmleu, Dmlys, Dmmet, Dmorn, Dmphe, Dmpro, Dmser, Dmthr, Dmtrp, Dmtyr, Dmval, Dnmala, Dnmarg, Dnmasn, Dnmasp, Dnmcys, Dnmgln, Dnmglu, Dnmhis, Dnmile, Dnmleu, Dnmlys, Dnmmet, Dnmorn, Dnmphe, Dnmpro, Dnmser, Dnmthr, Dnmtrp, Dnmtyr, Dnmval, Dorn, Dphe, Dpro, Dser, Dthr, Dtrp, Dtyr, Dval, Etg, Gabu, Gln, Glu, Gly, His, Hphe, Ile, Leu, Lys, Maabu, Maib, Mala, Manap, Marg, Masn, Masp, Mchexa, Mcpen, Mcys, Met, Metg, Mgabu, Mgln, Mglu, Mhis, Mhphe, Mile, Mleu, Mlys, Mmet, Mnle, Mnva, Morn,

Mpen, Mphe, Mpro, Mser, Mtbug, Mthr, Mtrp, Mtyr, Mval, Naeg, Nala, Narg, Nasn, Nasp, Nbhe, Nbhm, Nbmc, Ncbut, Ncdec, Ncdod, Nchep, Nchex, Ncoct, Ncpro, Ncund, Ncys, Ngln, Nglu, Nhhis, Nhser, Nhtrp, Nhtyr, Nile, Nle, Nleu, Nlys, Nmaabu, Nmaib, Nmala, Nmanap, Nmarg, Nmasn, Nmasp, Nmchexa, Nmcpen, Nmcys, Nmet, Nmetg, Nmgabu, Nmgln, Nmglu, Nmhis, Nmhphe, Nmile, Nmleu, Nmlys, Nmmet, Nmnle, Nmnva, Nmorn, Nmpen, Nmphe, Nmser, Nmtbug, Nmthr, Nmtrp, Nmtyr, Nmval, Nnbhe, Nnbhm, Norb, Norn, Nphe, Nthr, Nva, Nval, Orn, Pen, Phe, Pro, Ser, Tbug, Thr, Trp, Tyr, and Val for each of the monomers described in part A), the corresponding cyclic pentamers are prepared.

(C) Determination of Activity

Compounds prepared in parts (A) and (B) above were assayed for ETR_A as described above. The results for a selection of compounds were as follows:

X_1	X_2	X_3	X_4	X_5	IC50 (μM)
Dala	Dasp	Pro	Dval	Leu	>10.0
Dphe	Dasp	Pro	Dval	Leu	0.23
Dtyr	Dasp	Pro	Dval	Leu	0.67
Dhphe	Dasp	Pro	Dval	Leu	~1.0
Trp	Dasp	Pro	Dval	Leu	>10.0
Dleu	Dasp	Pro	Dval	Leu	3.1
Dtrp	Asp	Pro	Dval	Leu	1.1
Dtrp	Dasp	Dpro	Dval	Leu	1.4
Dtrp	Dasp	Pro	Dphe	Leu	0.82
Dtrp	Dasp	Pro	Dhph	Leu	0.30
Dtrp	Dasp	Pro	Val	Leu	1.2
Dtrp	Dasp	Pro	Dval	Nleu	0.05
Dtrp	Dasp	Pro	Dval	Nphe	0.05
Dtrp	Dasp	Pro	Dval	Phe	1.5
Dtrp	Dasp	Pro	Dval	Thr	0.67
Dtrp	Dasp	Pro	Nleu	Lval	0.034
Dtrp	Dasp	Pro	Nphe	Lval	0.12
Dleu	Val	Dpro	Asp	Trp	>10.0

Example 3

Endothelin Tripeptides

The following tripeptides were prepared as described in Example 1, Section A. The tripeptides were assayed for ETR_A receptor binding according to Example 1, Section B, using Sf9 cells expressing the human ETR_A utilizing the baculovirus expression system in place of the 3T3 cells in the assay. The following table contains the sequence of the tripeptides and their ability to inhibit endothelin-1 binding. (Note "Cpaa" refers to cyclopentane acetic acid.)

Sequence					% Inhib. @ 10 μM $HETR_A$
Cpaa	Nglu	Dmet	Dtrp	OH	74
Cpaa	Nala	Dtrp	Dtrp	OH	73
Cpaa	Dmet	Nchex	Dtyr	OH	73
Cpaa	Dphe	Nbhm	Dtyr	OH	72
Cpaa	Nhser	Dtrp	Dtrp	OH	71
Cpaa	Dmet	Ncpro	Dtyr	OH	70
Cpaa	Ngln	Dmet	Dtrp	OH	69
Cpaa	Nala	Dtyr	Dtrp	OH	68
Cpaa	Nasp	Dtyr	Dtrp	OH	67
Cpaa	Dmet	Nbhe	Dtyr	OH	67
Cpaa	Nasp	Nchex	Dtrp	OH	67
Cpaa	Nle	Nchex	Dtyr	OH	67
Cpaa	Nala	Dphe	Dtrp	OH	66

Cpaa	Nglu	Dtrp	Dtrp	OH	66
Cpaa	Nglu	Dmet	Dtrp	OH	66
Cpaa	Nasp	Dphe	Dtrp	OH	66
Cpaa	Ncpro	Dphe	Dtyr	OH	65
Cpaa	Nle	Nbhe	Dtyr	OH	65
Cpaa	Ngln	Dthr	Dtrp	OH	64
Cpaa	Nasp	Dser	Dtrp	OH	64
Cpaa	Nglu	Dthr	Dtrp	OH	64
Cpaa	Nle	Nbhm	Dtyr	OH	64
Cpaa	Dtrp	Nhtrp	Dtyr	OH	64
Cpaa	Nhser	Dphe	Dtrp	OH	63
Cpaa	Nasp	Nle	Dtrp	OH	63
Cpaa	Nala	Dser	Dtrp	OH	63
Cpaa	Nasp	Dthr	Dtrp	OH	63
Cpaa	Nasp	Dtrp	Dtrp	OH	62
Cpaa	Dtrp	Nphe	Dtyr	OH	62
Cpaa	Nhtrp	Dtrp	Dtyr	OH	62
Cpaa	Nle	Nleu	Dtyr	OH	62
Cpaa	Narg	Dtyr	Dtrp	OH	61
Cpaa	Nglu	Nhtrp	Dtrp	OH	61
Cpaa	Nala	Nle	Dtrp	OH	61
Cpaa	Dser	Nbhe	Dtyr	OH	61

Cpaa	Dphe	Ncpro	Dtyr	OH	61
Cpaa	Dtrp	Nbhe	Dtyr	OH	61
Cpaa	Nchex	Dtyr	Dtyr	OH	61
Cpaa	Nglu	Nphe	Dtrp	OH	60
Cpaa	Nala	Dmet	Dtrp	OH	60
Cpaa	Dser	Nhtrp	Dtyr	OH	60
Cpaa	Dser	Nphe	Dtyr	OH	60
Cpaa	Nleu	Nle	Dtyr	OH	60
Cpaa	Nglu	Nbhe	Dtrp	OH	60
Cpaa	Dtrp	Nbhm	Dtyr	OH	60
Cpaa	Narg	Dphe	Dtrp	OH	60
Cpaa	Ngln	Dtrp	Dtrp	OH	59
Cpaa	Nlys	Dtrp	Dtrp	OH	59
Cpaa	Narg	Dtrp	Dtrp	OH	59
Cpaa	Dphe	Nhtrp	Dtyr	OH	59
Cpaa	Dtrp	Ncpro	Dtyr	OH	59
Cpaa	Nhser	Nle	Dtrp	OH	59
Cpaa	Dmet	Nphe	Dtyr	OH	59
Cpaa	Nglu	Nle	Dtrp	OH	59
Cpaa	Narg	Dthr	Dtrp	OH	59
Cpaa	Nglu	Nleu	Dtrp	OH	59
Cpaa	Ngln	Dphe	Dtrp	OH	59

Cpaa	Nbhe	Nleu	Dtyr	OH	59
Cpaa	Nle	Nhtrp	Dtyr	OH	59
Cpaa	Dser	Ncpro	Dtyr	OH	59
Cpaa	Nglu	Dphe	Dtrp	OH	58
Cpaa	Dtyr	Nphe	Dtyr	OH	58
Cpaa	Nhtrp	Nle	Dtyr	OH	58
Cpaa	Nlys	Dphe	Dtrp	OH	58
Cpaa	Dtyr	Nchex	Dtyr	OH	58
Cpaa	Nglu	Nbhm	Dtrp	OH	58
Cpaa	Nglu	Dser	Dtrp	OH	58
Cpaa	Dphe	Nbhe	Dtyr	OH	58
Cpaa	Dphe	Nphe	Dtyr	OH	58
Cpaa	Ncpro	Dile	Dtrp	OH	58
Cpaa	Nphe	Dphe	Dtyr	OH	57
Cpaa	Nglu	Nchex	Dtrp	OH	57
Cpaa	Dphe	Nleu	Dtyr	OH	57
Cpaa	Nhser	Dtyr	Dtrp	OH	57
Cpaa	Nle	Ncpro	Dtyr	OH	57
Cpaa	Nhtrp	Dphe	Dtyr	OH	57
Cpaa	Ngln	Nle	Dtrp	OH	56
Cpaa	Nlys	Nle	Dtrp	OH	56
Cpaa	Dtyr	Nbhm	Dtyr	OH	56

Cpaa	Nglu	Ncpro	Dtrp	OH	56
Cpaa	Nle	Nphe	Dtyr	OH	56
Cpaa	Nbhe	Nhtrp	Dtyr	OH	56
Cpaa	Nhtrp	Nbhm	Dtyr	OH	56
Cpaa	Nglu	Dtyr	Dtrp	OH	55
Cpaa	Nchex	Nbhm	Dtyr	OH	55
Cpaa	Dtrp	Nleu	Dtyr	OH	55
Cpaa	Nbhm	Dphe	Dtyr	OH	55
Cpaa	Dphe	Nchex	Dtyr	OH	55
Cpaa	Nbhm	Dtyr	Dtyr	OH	55
Cpaa	Nhtrp	Dmet	Dtyr	OH	54
Cpaa	Nbhe	Ncpro	Dtyr	OH	54
Cpaa	Dser	Nleu	Dtyr	OH	54
Cpaa	Narg	Dmet	Dtrp	OH	53
Cpaa	Dtyr	Nbhe	Dtyr	OH	53
Cpaa	Dser	Nchex	Dtyr	OH	53
Cpaa	Dthr	Nphe	Dtyr	OH	53
Cpaa	Nhtrp	Nbhe	Dtyr	OH	53
Cpaa	Narg	Dser	Dtrp	OH	53
Cpaa	Nbhe	Dmet	Dtyr	OH	52
Cpaa	Narg	Nle	Dtrp	OH	52
Cpaa	Dser	Nbhm	Dtyr	OH	52

Cpaa	Nbhe	Nbhe	Dtyr	OH	52
Cpaa	Dtyr	Ncpro	Dtyr	OH	52
Cpaa	Nchex	Nleu	Dtyr	OH	52
Cpaa	Nlys	Dmet	Dtrp	OH	52
Cpaa	Nhtrp	Dser	Dtyr	OH	51
Cpaa	Nphe	Dtrp	Dtyr	OH	51
Cpaa	Nlys	Dthr	Dtrp	OH	51
Cpaa	Nphe	Nle	Dtyr	OH	50
Cpaa	Nbhm	Dmet	Dtyr	OH	50
Cpaa	Nala	Dthr	Dtrp	OH	50
Cpaa	Nlys	Dtyr	Dtrp	OH	50

Example 4

Linear Tripeptides

The following tripeptides were prepared as described in Example 1, Section A, and assayed for mouse ETR_A binding according to Example 1, Section B. Sf9 cells expressing the human ETR_A utilizing the baculovirus expression system were used place of the 3T3 cells in the assay. The sequence of the tripeptides and the ability to inhibit endothelin-1 binding is as follows:

Sequence					% Inhib. @ 1 μM $METR_A$	% Inhib. @ 1 μM $HETR_A$	IC_{50} $HETR_A$ (nM)
Cpaa	His	Dtrp	Dtrp	OH	83.6	92.8	82
Cpaa	Gln	Dtrp	Dtrp	OH	66.2	79.0	374
Cpaa	Trp	Dtrp	Dtrp	OH	64.7	46.9	
Cpaa	Leu	Dthr	Dtrp	OH	74.1	69.7	328
Cpaa	Leu	Dtrp	Met	OH	82.6	74.5	694
Cpaa	Leu	Dtrp	Tyr	OH	80.2	83.0	132
Cpaa	Hphe	Dtrp	βala	OH	61.3	57.4	

WHAT IS CLAIMED:

1. A compound of the formula:

$$X_N\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_C,$$

where X_N is acyl or other N-terminal group, a polypeptide of 1-50 amino acids, or a bond; X_C is OH or other C-terminal group, a polypeptide of 1-50 amino acids or a protein, or a bond; X_1-X_3 are each independently a peptide or peptoid monomer, and X_4-X_6 are each independently a peptide or peptoid monomer, or a bond, and at least one of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc.

2. The compound of claim 1, wherein X_1, X_2, X_3, X_4, X_5, and X_6 are each independently selected from the group consisting of Aabu, Aib, Ala, Anap, Arg, Asn, Asp, Chexa, Cpen, Cpro, Cys, Dala, Darg, Dasn, Dasp, Dcys, Dgln, Dglu, Dhis, Dile, Dleu, Dlys, Dmala, Dmarg, Dmasn, Dmasp, Dmcys, Dmet, Dmgln, Dmglu, Dmhis, Dmile, Dmleu, Dmlys, Dmmet, Dmorn, Dmphe, Dmpro, Dmser, Dmthr, Dmtrp, Dmtyr, Dmval, Dnmala, Dnmarg, Dnmasn, Dnmasp, Dnmcys, Dnmgln, Dnmglu, Dnmhis, Dnmile, Dnmleu, Dnmlys, Dnmmet, Dnmorn, Dnmphe, Dnmpro, Dnmser, Dnmthr, Dnmtrp, Dnmtyr, Dnmval, Dorn, Dphe, Dpro, Dser, Dthr, Dtrp, Dtyr, Dval, Etg, Gabu, Gln, Glu, Gly, His, Hphe, Ile, Leu, Lys, Maabu, Maib, Mala, Manap, Marg, Masn, Masp, Mchexa, Mcpen, Mcys, Met, Metg, Mgabu, Mgln, Mglu, Mhis, Mhphe, Mile, Mleu, Mlys, Mmet, Mnle, Mnva, Morn, Mpen, Mphe, Mpro, Mser, Mtbug, Mthr, Mtrp, Mtyr, Mval, Naeg, Nala, Narg, Nasn, Nasp, Nbhe, Nbhm, Nbmc, Ncbut, Ncdec, Ncdod, Nchep, Nchex, Ncoct, Ncpro, Ncund, Ncys, Ngln, Nglu, Nhhis, Nhser, Nhtrp, Nhtyr, Nile, Nle, Nleu, Nlys, Nmaabu, Nmaib, Nmala, Nmanap, Nmarg, Nmasn, Nmasp, Nmchexa, Nmcpen, Nmcys, Nmet, Nmetg, Nmgabu, Nmgln, Nmglu, Nmhis, Nmhphe, Nmile, Nmleu, Nmlys, Nmmet, Nmnle, Nmnva, Nmorn, Nmpen, Nmphe, Nmser, Nmtbug, Nmthr, Nmtrp, Nmtyr, Nmval, Nnbhe, Nnbhm, Norb, Norn, Nphe, Nthr, Nva, Nval, Orn, Pen, Phe, Pro, Ser, Tbug, Thr, Trp, Tyr, and Val.

3. The compound of claim 1, wherein X_1 is selected from the group consisting of Asp, Dphe, Dtrp, Dtyr, Gln, Gly, and Ile.

4. The compound of claim 3, wherein X_3 is selected from the group consisting of Asp and Dasp.

5. The compound of claim 4, wherein X_4 and X_5 are each independently selected from the group consisting of Aabu, Ala, Dile, Dmet, Dval, Ile, Met, Nle, Trp, and Val.

6. The compound of claim 5, wherein X_6 is selected from the group consisting of Dtrp, Gly, and Trp.

7. The compound of claim 6, wherein X_2 is selected from the group consisting of Aabu, Ala, Arg, Asn, Asp, Cys, Darg, Dasn, Dcys, Dgln, Dglu, Dorn, Dphe, Dphe, Dser, Dtyr, Dval, Gabu, Gly, His, His, Hphe, Ile, Leu, Lys, Nasp, Nglu, Naeg, Nleu, Nphe, Nva, Orn, Pro, Ser, Thr, Trp, Tyr, and Val.

8. A compound is selected from the group consisting of Dphe-Ala-Asp-Ile-Ile-Trp, Dphe-Asn-Asp-Ile-Ile-Trp, Dphe-Cys-Asp-Ile-Ile-Trp, Dphe-Dcys-Asp-Ile-Ile-Trp, Dphe-Dorn-Asp-Dile-Dile-Dtrp, Dphe-Dorn-Asp-Dile-Ile-Dtrp, Dphe-Dorn-Asp-Ile-Ile-Trp, Dphe-Dorn-Dasp-Dile-Ile-Dtrp, Dphe-Dorn-Dasp-Ile-Ile-Trp, Dphe-Dphe-Asp-Ile-Ile-Trp, Dphe-Dtyr-Asp-Ile-Ile-Trp, Dphe-Hphe-Asp-Ile-Ile-Trp, Dphe-Nglu-Asp-Ile-Ile-Trp, Dphe-Nleu-Asp-Ile-Ile-Trp, Dphe-Nphe-Asp-Ile-Ile-Trp, Dphe-Orn-Asp-Dile-Ile-Trp, Dphe-Orn-Asp-Ile-Ile-Trp, Dphe-Orn-Asp-Ile-Dile-Dtrp, Dphe-Orn-Asp-Ile-Ile-Dtrp, Dphe-Orn-Asp-Ile-Dile-Trp, Dphe-Orn-Asp-Nva-Ile-Trp, Dphe-Orn-Dasp-Ile-Dile-Trp, Dphe-Orn-Dasp-Ile-Ile-Trp, Dphe-Phe-Asp-Ile-Ile-Trp, Dphe-Pro-Asp-Ile-Ile-Trp, Dphe-Trp-Asp-Ile-Ile-Trp, Dphe-Tyr-Asp-Ile-Ile-Trp, Dtrp-Nphe-Asp-Ile-Ile-Trp, Dtrp-Orn-Asp-Ile-Ile-Trp, Dtyr-Orn-Asp-Ile-Ile-Trp, Phe-Dorn-Dasp-Dile-Ile-Trp, Phe-Orn-Asp-Ile-Ile-Trp, and Phe-Orn-Dasp-Ile-Ile-Trp.

9. The compound of claim 1, wherein

X_N and X_6-X_C together form a bond;

X_1-X_5 are each independently a peptide or peptoid monomer, and at least one of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc.

10. The compound of claim 9, wherein

X_N and X_6-X_C together form a bond;

X_1 is Dtrp or Nhtrp;

X_2 is Dasp or Nasp;

X_3 is Pro; and

X_4 and X_5 are each independently selected from the group consisting of Nala, Nasp, Nglu, Naeg, Nphe, Nhhis, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nval, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc.

11. The compound of claim 9, wherein

X_1 is Dtrp;

X_2 is Dasp;

X_4 is Nleu or Nphe; and

X_5 is Lval.

12. The compound of claim 9, wherein

X_1 is Dtrp;

X_2 is Dasp;

X_4 is Dval; and

X_5 is Nleu or Nphe.

13. The compound of claim 1, wherein

X_5-X_6 is a bond;

X_2 is Lval; and

X_3 is Dtrp.

14. The compound of claim 1, wherein

X_4-X_5-X_6 is a bond;

X_1 is Leu or X_X;

X_2 is Dtrp or X_X; and

X_3 is βala, Dtrp, or X_X, where

X_X is selected from the group consisting of Aabu, Aib, Ala, Anap, Arg, Asn, Asp, Chexa, Cpen, Cpro, Cys, Dala, Darg, Dasn, Dasp, Dcys, Dgln, Dglu, Dhis, Dile, Dleu, Dlys, Dmala, Dmarg, Dmasn, Dmasp, Dmcys, Dmet, Dmgln, Dmglu, Dmhis, Dmile, Dmleu, Dmlys, Dmmet, Dmorn, Dmphe, Dmpro, Dmser, Dmthr, Dmtrp, Dmtyr, Dmval, Dnmala, Dnmarg, Dnmasn, Dnmasp, Dnmcys, Dnmgln, Dnmglu, Dnmhis, Dnmile, Dnmleu, Dnmlys, Dnmmet, Dnmorn, Dnmphe, Dnmpro, Dnmser, Dnmthr, Dnmtrp, Dnmtyr, Dnmval, Dorn, Dphe, Dpro, Dser, Dthr, Dtrp, Dtyr, Dval, Etg, Gabu, Gln, Glu, Gly, His, Hphe, Ile, Leu, Lys, Maabu, Maib, Mala, Manap, Marg, Masn, Masp, Mchexa, Mcpen, Mcys, Met, Metg, Mgabu, Mgln, Mglu, Mhis, Mhphe, Mile, Mleu, Mlys, Mmet, Mnle, Mnva, Morn, Mpen, Mphe, Mpro, Mser, Mtbug, Mthr, Mtrp, Mtyr, Mval, Naeg, Nala, Narg, Nasn, Nasp, Nbhe, Nbhm, Nbmc, Ncbut, Ncdec, Ncdod, Nchep, Nchex, Ncoct, Ncpro, Ncund, Ncys, Ngln, Nglu, Nhhis, Nhser, Nhtrp, Nhtyr, Nile, Nle, Nleu, Nlys, Nmaabu, Nmaib, Nmala, Nmanap, Nmarg, Nmasn, Nmasp, Nmchexa, Nmcpen, Nmcys, Nmet, Nmetg, Nmgabu, Nmgln, Nmglu, Nmhis, Nmhphe, Nmile, Nmleu, Nmlys, Nmmet, Nmnle, Nmnva, Nmorn, Nmpen, Nmphe, Nmser, Nmtbug, Nmthr, Nmtrp, Nmtyr, Nmval, Nnbhe, Nnbhm, Norb, Norn, Nphe, Nthr, Nva, Nval, Orn, Pen, Phe, Pro, Ser, Tbug, Thr, Trp, Tyr, and Val, wherein only one of X_1, X_2, and X_3 is X_X.

15. A method for treating an indication modulated by endothelin in a mammal, which method comprises:

administering to a mammal in need thereof a compound of the formula

$$X_N\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_C,$$

where X_N is acyl or other N-terminal group, a polypeptide of 1-50 amino acids, or a bond; X_C is OH or other C-terminal group, a polypeptide of 1-50 amino acids or a protein, or a bond; X_1-X_3 are each independently a peptide or peptoid monomer, and X_4-X_6 are each independently a peptide or peptoid monomer, or a bond, and at least one

of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc.

16. The method of claim 15, wherein X_1-X_2-X_3-X_4-X_5-X_6 is selected from the group consisting of Dtrp-Nphe-Asp-Ile-Ile-Trp, Dphe-Nphe-Asp-Ile-Ile-Trp, Dtrp-Orn-Asp-Ile-Ile-Trp, Dtyr-Orn-Asp-Ile-Ile-Trp, Dphe-Pro-Asp-Ile-Ile-Trp, Dphe-Ala-Asp-Ile-Ile-Trp, Dphe-Hphe-Asp-Ile-Ile-Trp, Dphe-Asn-Asp-Ile-Ile-Trp, Dphe-Tyr-Asp-Ile-Ile-Trp, Dphe-Trp-Asp-Ile-Ile-Trp, Dphe-Dphe-Asp-Ile-Ile-Trp, Dphe-Dtyr-Asp-Ile-Ile-Trp, Dphe-Orn-Asp-Nva-Ile-Trp, Dphe-Orn-Asp-Ile-Ile-Trp, Dphe-Phe-Asp-Ile-Ile-Trp, Dphe-Nleu-Asp-Ile-Ile-Trp, Dphe-Cys-Asp-Ile-Ile-Trp, Dphe-Nglu-Asp-Ile-Ile-Trp, Dphe-Dcys-Asp-Ile-Ile-Trp, and Dphe-Orn-Asp-Ala-Ile-Trp.

17. The method of claim 15, wherein

X_N and X_6-X_C together form a bond;

X_1-X_5 are each independently a peptide or peptoid monomer, and at least one of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc.

18. The method of claim 17, wherein

X_1 is Dtrp, X_2 is Dasp, X_3 is Pro, X_4 is Nleu or Nphe, and X_5 is Dval; or

X_1 is Dtrp, X_2 is Dasp, X_3 is Pro, X_4 is Dval, and X_5 is Nleu or Nphe.

19. A pharmaceutical composition for treating an indication modulated by endothelin in a mammal, wherein said composition comprises:

an effective amount of a compound of the formula

$$X_N\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_C,$$

where X_N is acyl or other N-terminal group, a polypeptide of 1-50 amino acids, or a bond; X_C is OH or other C-terminal group, a polypeptide of 1-50 amino acids or a protein, or a bond; X_1-X_3 are each independently a peptide or peptoid monomer, and

X_4-X_6 are each independently a peptide or peptoid monomer, or a bond, and at least one of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc; and

a pharmaceutically acceptable excipient.

20. The composition of claim 19, wherein X_1-X_2-X_3-X_4-X_5-X_6 is selected from the group consisting of Dtrp-Nphe-Asp-Ile-Ile-Trp, Dphe-Nphe-Asp-Ile-Ile-Trp, Dtrp-Orn-Asp-Ile-Ile-Trp, Dphe-Pro-Asp-Ile-Ile-Trp, Dphe-Ala-Asp-Ile-Ile-Trp, Dphe-Hphe-Asp-Ile-Ile-Trp, Dphe-Asn-Asp-Ile-Ile-Trp, Dphe-Tyr-Asp-Ile-Ile-Trp, Dphe-Trp-Asp-Ile-Ile-Trp, Dphe-Dphe-Asp-Ile-Ile-Trp, Dphe-Dtyr-Asp-Ile-Ile-Trp, Dphe-Orn-Asp-Nva-Ile-Trp, Dphe-Orn-Asp-Ile-Ile-Trp, Dphe-Phe-Asp-Ile-Ile-Trp, Dphe-Nleu-Asp-Ile-Ile-Trp, Dphe-Cys-Asp-Ile-Ile-Trp, Dphe-Nglu-Asp-Ile-Ile-Trp, Dphe-Dcys-Asp-Ile-Ile-Trp, and Dphe-Orn-Asp-Ala-Ile-Trp.

21. The composition of claim 19, wherein

X_N and X_6-X_C together form a bond;

X_1-X_5 are each independently a peptide or peptoid monomer, and at least one of X_1-X_5 is selected from the group consisting of Nglu, Naeg, Nphe, Nile, Nlys, Nleu, Nmet, Nasn, Ngln, Narg, Nhser, Nthr, Nhtrp, Nhtyr, Norn, Nbhm, Nbhe, Nnbhm, Nnbhe, and Nbmc.

22. The composition of claim 21, wherein

X_1 is Dtrp, X_2 is Dasp, X_3 is Pro, X_4 is Nleu or Nphe, and X_5 is Dval; or

X_1 is Dtrp, X_2 is Dasp, X_3 is Pro, X_4 is Dval, and X_5 is Nleu or Nphe.

23. The compound of claim 11, wherein X_3 is Pro.

24. The compound of claim 12, wherein X_3 is Pro.

25. The compound of claim 1, wherein

X_N and X_6-$X_{c'}$ together form a bond;

X_1 is Nleu or Dasp;

X_2 is Dasp;

X_3 is Pro;

X_4 is Dval; and

X_5 is Nleu.

26. The compound of claim 1, wherein X_N and X_6-$X_{c'}$ together form a bond, wherein said compound is selected from the group consisting of Dphe-Dasp-Pro-Dval-Leu, Dtyr-Dasp-Pro-Dval-Leu, Dhphe-Dasp-Pro-Dval-Leu, Dleu-Dasp-Pro-Dval-Leu, Dtrp-Asp-Pro-Dval-Leu, Dtrp-Dasp-Dpro-Dval-Leu, Dtrp-Dasp-Pro-Dphe-Leu, Dtrp-Dasp-Pro-Dhph-Leu, Dtrp-Dasp-Pro-Val-Leu, Dtrp-Dasp-Pro-Dval-Phe, and Dtrp-Dasp-Pro-Dval-Thr.

27. A compound of the formula:

$$X_N\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_{c'},$$

wherein said compound is selected from the group consisting of Cpaa-Nglu-Dmet-Dtrp-OH, Cpaa-Nala-Dtrp-Dtrp-OH, Cpaa-Dmet-Nchex-Dtyr-OH, Cpaa-Dphe-Nbhm-Dtyr-OH, Cpaa-Nhser-Dtrp-Dtrp-OH, Cpaa-Dmet-Ncpro-Dtyr-OH, Cpaa-Ngln-Dmet-Dtrp-OH, Cpaa-Nala-Dtyr-Dtrp-OH, Cpaa-Nasp-Dtyr-Dtrp-OH, Cpaa-Dmet-Nbhe-Dtyr-OH, Cpaa-Nasp-Nchex-Dtrp-OH, Cpaa-Nle-Nchex-Dtyr-OH, Cpaa-Nala-Dphe-Dtrp-OH, Cpaa-Nglu-Dtrp-Dtrp-OH, Cpaa-Nglu-Dmet-Dtrp-OH, Cpaa-Nasp-Dphe-Dtrp-OH, Cpaa-Ncpro-Dphe-Dtyr-OH, Cpaa-Nle-Nbhe-Dtyr-OH, Cpaa-Ngln-Dthr-Dtrp-OH, Cpaa-Nasp-Dser-Dtrp-OH, Cpaa-Nglu-Dthr-Dtrp-OH, Cpaa-Nle-Nbhm-Dtyr-OH, Cpaa-Dtrp-Nhtrp-Dtyr-OH, Cpaa-Nhser-Dphe-Dtrp-OH, Cpaa-Nasp-Nle-Dtrp-OH, Cpaa-Nala-Dser-Dtrp-OH, Cpaa-Nasp-Dthr-Dtrp-OH, Cpaa-Nasp-Dtrp-Dtrp-OH, Cpaa-Dtrp-Nphe-Dtyr-OH, Cpaa-Nhtrp-Dtrp-Dtyr-OH, Cpaa-Nle-Nleu-Dtyr-OH, Cpaa-Narg-Dtyr-Dtrp-OH, Cpaa-Nglu-Nhtrp-Dtrp-OH, Cpaa-Nala-Nle-Dtrp-OH, Cpaa-Dser-Nbhe-Dtyr-OH, Cpaa-Dphe-Ncpro-Dtyr-OH, Cpaa-Dtrp-Nbhe-Dtyr-OH, Cpaa-Nchex-Dtyr-Dtyr-OH, Cpaa-Nglu-Nphe-Dtrp-OH, Cpaa-Nala-Dmet-Dtrp-OH, Cpaa-Dser-Nhtrp-Dtyr-OH, Cpaa-Dser-

Nphe-Dtyr-OH, Cpaa-Dleu-Nle-Dtyr-OH, Cpaa-Nglu-Nbhe-Dtrp-OH, Cpaa-Dtrp-Nbhm-Dtyr-OH, Cpaa-Narg-Dphe-Dtrp-OH, Cpaa-Ngln-Dtrp-Dtrp-OH, Cpaa-Nlys-Dtrp-Dtrp-OH, Cpaa-Narg-Dtrp-Dtrp-OH, Cpaa-Dphe-Nhtrp-Dtyr-OH, Cpaa-Dtrp-Ncpro-Dtyr-OH, Cpaa-Nhser-Nle-Dtrp-OH, Cpaa-Dmet-Nphe-Dtyr-OH, Cpaa-Nglu-Nle-Dtrp-OH, Cpaa-Narg-Dthr-Dtrp-OH, Cpaa-Nglu-Nleu-Dtrp-OH, Cpaa-Ngln-Dphe-Dtrp-OH, Cpaa-Nbhe-Nleu-Dtyr-OH, Cpaa-Nle-Nhtrp-Dtyr-OH, Cpaa-Dser-Ncpro-Dtyr-OH, Cpaa-Nglu-Dphe-Dtrp-OH, Cpaa-Dtyr-Nphe-Dtyr-OH, Cpaa-Nhtrp-Nle-Dtyr-OH, Cpaa-Nlys-Dphe-Dtrp-OH, Cpaa-Dtyr-Nchex-Dtyr-OH, Cpaa-Nglu-Nbhm-Dtrp-OH, Cpaa-Nglu-Dser-Dtrp-OH, Cpaa-Dphe-Nbhe-Dtyr-OH, Cpaa-Dphe-Nphe-Dtyr-OH, Cpaa-Ncpro-Dile-Dtrp-OH, Cpaa-Nphe-Dphe-Dtyr-OH, Cpaa-Nglu-Nchex-Dtrp-OH, Cpaa-Dphe-Nleu-Dtry-OH, Cpaa-Nhser-Dtyr-Dtrp-OH, Cpaa-Nle-Ncpro-Dtyr-OH, Cpaa-Nhtrp-Dphe-Dtyr-OH, Cpaa-Ngln-Nle-Dtrp-OH, Cpaa-Nlys-Nle-Dtrp-OH, Cpaa-Dtyr-Nbhm-Dtyr-OH, Cpaa-Nglu-Ncpro-Dtrp-OH, Cpaa-Nle-Nphe-Dtyr-OH, Cpaa-Nbhe-Nhtrp-Dtyr-OH, Cpaa-Nhtrp-Nbhm-Dtyr-OH, Cpaa-Nglu-Dtyr-Dtrp-OH, Cpaa-Nchex-Nbhm-Dtyr-OH, Cpaa-Dtrp-Nleu-Dtyr-OH, Cpaa-Nbhm-Dphe-Dtyr-OH, Cpaa-Dphe-Nchex-Dtyr-OH, Cpaa-Nbhm-Dtyr-Dtyr-OH, Cpaa-Nhtrp-Dmet-Dtyr-OH, Cpaa-Nbhe-Ncpro-Dtyr-OH, Cpaa-Dser-Nleu-Dtyr-OH, Cpaa-Narg-Dmet-Dtrp-OH, Cpaa-Dtyr-Nbhe-Dtyr-OH, Cpaa-Dser-Nchex-Dtyr-OH, Cpaa-Dthr-Nphe-Dtyr-OH, Cpaa-Nhtrp-Nbhe-Dtyr-OH, Cpaa-Narg-Dser-Dtrp-OH, Cpaa-Nbhe-Dmet-Dtyr-OH, Cpaa-Narg-Nle-Dtrp-OH, Cpaa-Dser-Nbhm-Dtyr-OH, Cpaa-Nbhe-Nbhe-Dtyr-OH, Cpaa-Dtyr-Ncpro-Dtyr-OH, Cpaa-Nchex-Nleu-Dtyr-OH, Cpaa-Nlys-Dmet-Dtrp-OH, Cpaa-Nhtrp-Dser-Dtyr-OH, Cpaa-Nphe-Dtrp-Dtyr-OH, Cpaa-Nlys-Dthr-Dtrp-OH, Cpaa-Nphe-Nle-Dtyr-OH, Cpaa-Nbhm-Dmet-Dtyr-OH, Cpaa-Nala-Dthr-Dtrp-OH, Cpaa-Nlys-Dtyr-Dtrp-OH, Cpaa-His-Dtrp-Dtrp-OH, Cpaa-Gln-Dtrp-Dtrp-OH, Cpaa-Trp-Dtrp-Dtrp-OH, Cpaa-Leu-Dthr-Dtrp-OH, Cpaa-Leu-Dtrp-Met-OH, Cpaa-Leu-Dtrp-Tyr-OH, and Cpaa-Hphe-Dtrp-βala-OH.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 93/07166

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07K5/08 C07K5/10 C07K5/12 C07K7/06 C07K7/08
C07K7/10 C07K7/64 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,91 19735 (P.A. BARTLETT AND D.V. SANTI) 26 December 1991 cited in the application see page 15, line 1 - page 16, line 22; claims 1-4,22,23,25,26; examples 6,9 see page 25, line 20 - line 34 ---	1-7,9-14
X	EP,A,0 436 189 (BANYU PHARMACEUTICAL CO., LTD.) 10 July 1991 see page 4, line 12 - line 53; claims; examples 30,73,78,83 see examples 85-88,90-93 see examples 95-96 --- -/--	1-3,9, 14,15, 17,19, 21,26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1993	21 -12- 1993

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 93/07166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,92 20706 (WARNER-LAMBERT COMPANY) 26 November 1992 see claims 1,5	1,8,15, 16,19,20
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 35, no. 9 , 1 May 1992 , WASHINGTON US pages 1493 - 1508 A.M.DOHERTY 'Endothelin: A new Challenge' cited in the application see page 1504, left column, paragraph 2 - page 1508, left column, paragraph 2	1

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the extremely large number of compounds falling under claims 1-14 and 23-27, the ISA considers that it is not economically reasonable to draw up a search report covering all compounds 'per se' (see Article 17.2aii). The search has therefore been limited to the examples given in the description and extended to compounds having the alleged endothelin receptor binding activity.

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 93/07166

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 15 and the dependent claims 16-18 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see annex

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/US 93/07166

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9119735	26-12-91	EP-A-	0535155	07-04-93
EP-A-0436189	10-07-91	AU-B-	632193	17-12-92
		AU-A-	6828590	11-07-91
		JP-A-	4261198	17-09-92
		US-A-	5114918	19-05-92
WO-A-9220706	26-11-92	NONE		